

Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 1, 2, 8, 12, 14, 15, 17, 19, 24, 25, 35, 48, 115, 118, 119, 122, 123, 125, 130, 131, 133-136, 139, 144-154, 157 and 161 are pending in the application. Claims 3, 5, 13, 16, 18, 20-23, 26-34, 36-47, 49-112, 114, 116, 117, 120, 121, 124, 126, 128, 132, 137, 138, 140-143 and 159-160 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 4, 6, 7, 9-11, 113, 127, 129, 155, 156 and 158 have been withdrawn from consideration by the Examiner.

Support for amended claim 1, 122 and 123 can be found throughout the originally filed claims and specification including, *inter alia*, in original claims 120, 124, 126, 159 and 160. The amendment to claim 2 is sought to correct a minor typographical error. The amendment to claim 161 is sought to revise claim dependency upon cancellation of claim 160. New claims 162-167 are sought to be added; support for these new claims can be found in the specification and claims as filed. For example, support for claims 162 and 163 can be found in original claims 33 and 42; support for claims 164 and 167 can be found throughout the originally filed claims; and support for claims 165 and 166 can be found in paragraphs [0219-0220] of the specification.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

III. The Rejections Under 35 U.S.C. §103(a) Are Traversed

A. The Rejection Under 35 U.S.C. § 103(a) Over Kozłowska, Krieg, Stoll, Bachmann *et al.* and Carson *et al.*

In the Office Action at pages 3-5, the Examiner has rejected claims 1, 2, 8, 12, 14, 15, 17, 21, 24, 25, 35, 48, 115, 118, 120, 122-126, 130, 131, 133-136, 139, 144-154, 157 and 159-161 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozłowska *et al.* (*Intervirology* 39:9-15 (1996)), Krieg *et al.* (U.S. Patent Publication No. 2003/0050263), Stoll *et al.* (*J. Biol. Chem* 252:990-993 (1977)), Bachmann *et al.* (U.S. Patent Publication No. 2003/0099668) and Carson *et al.* (WO 97/28259). Applicants respectfully disagree with the Examiner's contentions and conclusions.

Solely to advance prosecution, however, and not in acquiescence to the aforementioned rejections, claim 1 is now sought to be amended. The present claims thus recite composition comprising a virus-like particle wherein said virus-like particle is a virus-like particle of an RNA-bacteriophage; at least one immunostimulatory substance; and at least one antigen or antigenic determinant; wherein said at least one antigen or antigenic determinant is bound to said virus-like particle, wherein said immunostimulatory substance is packaged into said virus-like particle, wherein said immunostimulatory substance is an unmethylated CpG-containing oligonucleotide, and wherein said antigen comprises at least one HIV polypeptide.

Applicants respectfully submit that the references cited by the Examiner in making the present obviousness rejection, viewed alone or in combination, neither disclose nor suggest all of the elements of the present claims. In particular, the cited references do not disclose or suggest a composition comprising at least one immunostimulatory substance which is an unmethylated CpG-containing oligonucleotide packaged into a virus-like particle of an RNA-bacteriophage.

The presently claimed invention provides for compositions wherein immunostimulatory substances such as unmethylated CpG-containing oligonucleotide when packaged into VLPs retain their immunostimulatory capacity without widespread activation of the innate immune system. Furthermore the presently claimed compositions are more immunogenic than their CpG-free counterparts and induce enhanced B and T cell responses (for instance, see the present specification at Example 9 and Figure 15).

According to the presently claimed invention, the packaging of unmethylated CpG-containing oligonucleotide into virus-like particles renders these virus-like particles dramatically more immunogenic than their CpG-free counterparts (*cf.* WO 2004/084939 at page 5, lines 9-12, and US 2006/0210588 at paragraph [10019]). Furthermore, packaged unmethylated CpG-containing oligonucleotides are protected from degradation, i.e. they are more stable (*see, e.g.*, WO 2004/084939 at page 38, lines 21-22, and US 2006/0210588 at paragraph [10148]); and non-specific activation of cells from the innate immune system is dramatically reduced (*see, e.g.*, WO 2004/084939 at page 38, lines 23-24, and US 2006/0210588 at paragraph [10148]).

In fact, the present inventors were the first to package oligonucleotides into virus-like particles and to demonstrate the superior immunostimulatory effect of the resulting

compositions. These findings are confirmed by Storni et al., *J. Immunol.* 172:1777-1785 (2004), a copy of which is submitted herewith in the accompanying Second Supplemental Information Disclosure Statement. The authors demonstrated that the packaging of CpGs into virus-like particles is a simple and attractive method to reduce the drawbacks of CpGs, namely the unfavorable pharmacokinetics and systemic side effects, such as splenomegaly (*cf. id.*, page 1777, abstract, lines 3-6). Moreover, Storni et al. confirmed the dramatically higher immunostimulatory effect of CpGs which are packaged into a virus-like particle as compared to mere mixtures of both components (*cf. id.*, page 1780, 2nd column, 2nd paragraph, last section, and page 1781, Fig. 3C; ODNG3po of Storni et al. corresponds to SEQ ID NO:2 of the present application).

Applicants respectfully submit that the references cited by the Examiner in making the present obviousness rejection, viewed alone or in combination, neither disclose nor suggest all of the elements of the present claims. In particular, the cited references do not disclose or suggest a composition wherein the immunostimulatory substance is packaged into a VLP, as is required by the presently claimed invention.

Applicants respectfully assert that the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact

finders when resolving *Graham* inquiries has been emphasized by the Office within its published Examination Guidelines. See "Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc.*", *Fed. Reg.* 72:57526- 57535 (October 10, 2007), hereinafter "Examination Guidelines." Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination disclose all of the elements of the claims in its proper function, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result. In the present case, this burden has not been met.

As the Examiner concedes, Kozlovska *et al.* does not teach packaging immunostimulatory substance into a virus-like particle of an RNA-bacteriophage, and Applicants further submit that Kozlovska *et al.* do not teach that an unmethylated CpG-containing oligonucleotide immunostimulatory substance is packaged into the virus-like particle of an RNA-bacteriophage.

Further, Applicants also submit that Stoll *et al.* does not teach that the unmethylated CpG-containing oligonucleotide immunostimulatory substance is packaged into a virus-like particle of an RNA-bacteriophage.

Moreover, in making the obviousness objection, the Examiner cites Krieg *et al.* as a further reference, contending that:

Krieg *et al.* teaches the administration of unmethylated CpG nucleic acids to stimulate and enhance an immune response in a subject to treat HIV. In addition, Krieg *et al.* teaches that the CpG nucleic acids can be administered using any delivery vehicle known in the art, including virus-like particles (see paragraph [0129]).

Office action at page 4. Applicants respectfully disagree with the Examiner's assertions and contentions. Krieg *et al.* do not teach using a virus-like particle to deliver an immunostimulatory substance to the immune system. Furthermore, Krieg *et al.* do not provide any technical disclosure, especially not experimental data, as to how immunostimulatory nucleic acids could be delivered by virus-like particles. Krieg *et al.* merely provide an extensive list of delivery vehicles or delivery devices known in the art. Krieg *et al.* refer to two publications with regards to virus-like particles: 1) Jiang *et al.*, *Vaccine* 17: 1005-1013, 1999; hereinafter "Jiang *et al.*" and 2) Leibl *et al.*, *Vaccine* 16: 340-345, 1998; hereinafter "Leibl *et al.*" Virus-like particles are described in these documents either as antigens themselves (Jiang *et al.*) or as a delivery means for a model antigen (Leibl *et al.*). Neither Jiang *et al.* nor Leibl *et al.* mention the possibility of using virus-like particles as delivery vehicles or delivery devices for nucleic acids. Reviewing Krieg *et al.* in light of these two publications, Krieg *et al.*, at most, refer to virus-like particles as vehicles or devices for delivering antigen only, and not as vehicles or devices for delivering nucleic acids.

In addition to citing Kozlovska, Stoll and Krieg, the Examiner further cites Carson *et al.* and Bachmann *et al.* and contends that

Therefore, it would have been obvious to one of ordinary skill in the art to use SEQ 10 NO:10 in the virus-like particles of Kozlovska *et al.* and to modify the virus-like particles of Kozlovska *et al.* in order to package known immunostimulatory CpG nucleic acids such as those taught by Carson *et al.* and Bachmann *et al.*

Office action at page 4 (emphasis added). Applicants respectfully disagree with these contentions.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason or suggestion in the cited art that would have prompted one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absent such reason or suggestion, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). MPEP § 2143.01 (III) and (IV) states:

The mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)

* * *

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is **not** sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). ***>[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

KSR, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). (**emphasis added**)

Carson *et al.* does not disclose or suggest a composition wherein the unmethylated CpG-containing oligonucleotide immunostimulatory substance is packaged into a virus-like particle of an RNA-bacteriophage, as is required by the presently claimed invention. Furthermore, Carson *et al.* does not disclose methods for making such oligonucleotide-VLP compositions.

With regard to the cited reference Bachmann *et al.* (US 2003/0099668, referred to hereinafter as "the '668 application"), Applicants respectfully submit that the Examiner has erroneously cited this reference under 35 U.S.C. § 103(a), as the reference is not available as prior art against the present claims under any subsection of 35 U.S.C. § 102. Specifically, Applicants note that on October 11, 2007, submitted in the present matter was a declaration under 37 CFR 1.132 by Martin Bachmann, Alain Tissot and Edwin Meijerink, who are inventors common to the '668 application and to the present application. This declaration states that the subject matter common to both applications was invented solely by Martin Bachmann, Alain Tissot and Edwin Meijerink. Indeed, Applicants note that subsequent to submission of this declaration, the Examiner withdrew the only rejections under 35 U.S.C. §102 that had been based on the '668 application, stating that the withdrawal of these rejections was "in view of applicants' Declaration under 37 C.F.R. § 1.132." Office Action dated January 9, 2008, at page 3, final paragraph. Thus, Applicants respectfully submit that the '668 application does not qualify under any subsection of 35 U.S.C. § 102 as prior art against the presently claimed

invention, and therefore cannot be the basis of a rejection of the present claims under 35 U.S.C. § 103(a).

It is respectfully submitted that none of the cited references viewed alone or in combination, neither disclose nor suggest all of the elements of the previously pending claims nor of the present claims. For at least the foregoing reasons, the Examiner has not met the burden of establishing a *prima facie* case of obviousness and, therefore, the claims are not rendered obvious by the cited references. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

B. The Rejection Under 35 U.S.C. § 103(a) Over Renner, Krieg, Bachmann et al. and Carson et al.

In the Office Action at pages 6-8, the Examiner has rejected Claims 1, 2, 8, 12, 14, 15, 17, 21, 24, 25, 35, 48, 115, 118, 120, 122-126, 130, 131, 133-136, 139, 144-154, 157 and 159-161 are rejected under 35 U.S.C. 103(a) as being unpatentable over Renner et al. (WO 02/056905) and Krieg et al. (U.S. Patent Application No. 2003/0050263), Bachmann et al. (U.S. Patent Application No.2003/0099668) and Carson et al. (WO 97/28259). Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that this rejection has been based in part upon the '668 application of Bachmann et al. As noted above, the '668 application does not qualify as prior art against the presently claimed invention under any subsection of 35 U.S.C. § 102, and therefore cannot be the basis of a rejection of the present claims under 35 U.S.C. § 103(a). Accordingly, any portion of the present rejection that is based

upon application of the '668 application as prior art against the presently claimed invention is in error and must be withdrawn.

As the Examiner concedes, Renner *et al.* does not teach packaging immunostimulatory substances into a VLP. However, in making the obviousness objection, the Examiner cites Krieg *et al.*, Carson *et al.* and Bachmann *et al.* as further references and contends that:

It would have been obvious to one of ordinary skill in the art to modify the virus-like particles of Renner *et al.* in order to package known immunostimulatory CpG nucleic acids such as those taught by Carson *et al.* and Bachmann *et al.* One would have been motivated to do so given the suggestion by Krieg *et al.* that CpG nucleic acid can be delivered in virus-like particles and

Office action at page 7. Applicants respectfully disagree with the Examiner's assertions and contentions.

The Examiner provides no objective reasoning as to why a person of ordinary skill in the art would have combined Renner, Krieg, Bachmann *et al.* (even if Bachmann *et al.* was available as prior art to the present claims, which it is not) and Carson *et al.* to arrive at the presently claimed invention. The present claims recite an unmethylated CpG-containing oligonucleotide as an immunostimulatory substance. Moreover, the present claims recite that the unmethylated CpG-containing oligonucleotide immunostimulatory substance is packaged into a virus-like particle of an RNA-bacteriophage. As discussed above, each of these cited reference at best discloses only a small portion of present claim 1, but each of the references is severely deficient with respect to claim 1 as a whole. Moreover, the Examiner has failed to establish and articulate on the record the required nexus that would have given a person of ordinary

skill in the art reason to combine these references in order to make and use the presently claimed invention. Accordingly, these references cannot be properly combined in an attempt to render the present claims obvious.

Hence, it is submitted that the cited references, viewed alone or in combination, do not disclose or suggest all of the elements of the previously pending claims nor of the present claims. In particular, none of the references cited discloses or suggests a composition comprising at least one immunostimulatory substance, wherein said immunostimulatory substance is packaged into a VLP of an RNA-bacteriophage.

For at least the foregoing reasons, the Examiner has not met the burden of establishing a *prima facie* case of obviousness and, therefore, the claims are not rendered obvious by the cited references. Applicants respectfully request reconsideration and withdrawal of the rejection.

C. *The Second Rejection Under 35 U.S.C. § 103(a) Over Renner, Krieg, Bachmann et al. and Carson et al.*

In the Office Action at pages 8-10, the Examiner has again rejected Claims 1, 2, 8, 12, 14, 15, 17, 21, 24, 25, 35, 48, 115, 118, 120, 122-126, 130, 131, 133-136, 139, 144-154, 157 and 159-161 under 35 U.S.C. 103(a) as being unpatentable over Renner et al. (WO 02/056905) and Krieg et al. (U.S. Patent Application No. 2003/0050263), Bachmann et al. (U.S. Patent Application No.2003/0099668) and Carson et al. (WO 97/28259). In reviewing the text of this rejection, Applicants respectfully believe that this second rejection over the same references as that noted in section B above is simply a duplication of the first rejection over these references, as it appears that the text

of the rejection appearing at pages 8-10 of the present Office Action is substantially or entirely identical to the text of the rejection appearing at pages 6-8 of the present Office Action. Accordingly, Applicants respectfully traverse this rejection on at least the same grounds as those listed above for the rejection appearing at pages 6-8 of the present Office Action, and reiterate and incorporate by reference herein the remarks made above in section B of the present reply. Reconsideration and withdrawal of this rejection are respectfully requested.

IV. Obviousness-Type Double Patenting

At pages 10-11, claims 1, 2, 8, 21, 24, 25, 27, 30, 33, 35, 42, 48, 117, 122, 123, 124, 129, 131, 133-135, 139, 140, 142, 143, 145 and 146 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1, 10, 14-16, 41, 48 and 55 of copending application 10/563,944 ("the 944 application").

Applicants would like to draw the Examiner's attention to MPEP § 1490.V.D. which states that:

If two (or more) pending applications are filed, in *each* of which a rejection of one claimed invention over the other on the ground of provisional obvious-type double patenting (ODP) is proper, the ODP rejection will be made in each application. If the ODP rejection is the only rejection remaining in the earlier filed application of the two pending applications, (but the later-filed application is rejectable on other grounds), the examiner should then withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

The priority date of the '944 reference application used in making this obviousness-type double patenting rejection is July 10, 2003, i.e., about four months

after the priority date of the present application. Applicants believe that the amendments and arguments presented herein will place the present application in condition for allowance except for the obviousness-type double patenting rejection. Thus, Applicants respectfully request that the Examiner hold this rejection in abeyance until the arguments and amendments submitted herewith have been considered, and that the Examiner reconsider and withdraw this rejection upon finding the present claims otherwise allowable in accordance with MPEP § 1490.V.D.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read "B. Del Buono", with a stylized flourish at the end.

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